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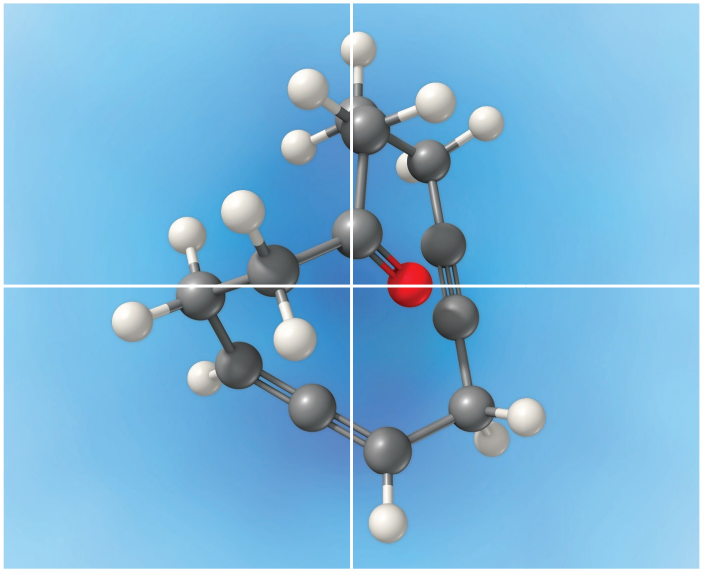

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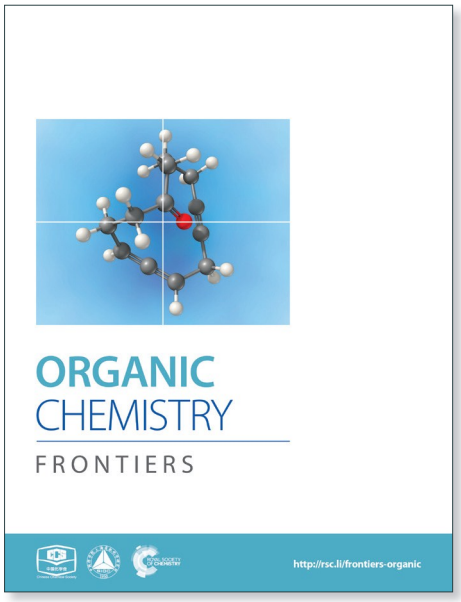

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Cationic Iridium-Catalyzed C-H Alkylation of 2-Substituted Pyridine *N*-Oxides with Acrylates

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Takanori Shibata[a,b] and Hideaki Takano[a]

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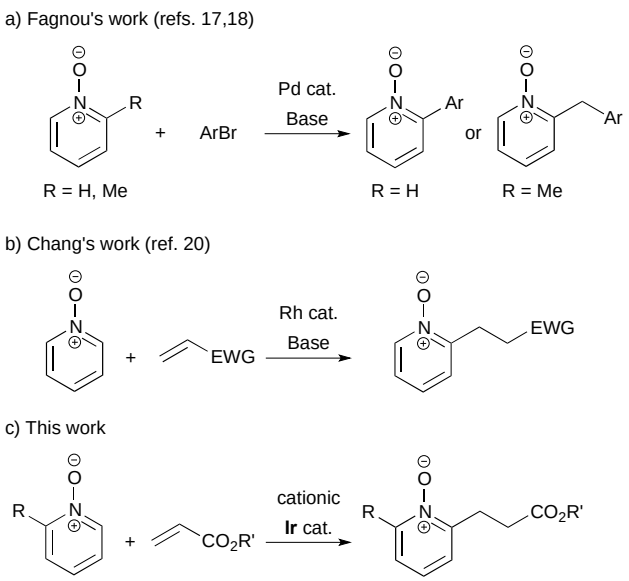
The reaction of 2-arylmethyl-, 2-aryl-, and 2-alkyl substituted pyridine *N*-oxides with acrylates proceeded in the presence of a cationic Ir-*rac*-BINAP catalyst under the heating conditions. Various 2,6-disubstituted pyridine *N*-oxides were obtained by C-H alkylation at the C6-position.

Introduction

The transition metal-catalyzed synthetic transformations initiated by C-H bond cleavage have become a core strategy in organic synthesis.[1] Among various types of C-H bond functionalization, *ortho*-selective arene C-H bond activation using directing groups is an established protocol. In particular, C-H alkylation using alkenes is more atom-economical than using alkyl halides and alkyl metallic species, because there is no atom loss through transformation. From a historical point of view, Lewis's work of hydroxyl-directed Ru-catalyzed reaction using ethylene was the first example,[2] while, from the synthetic point of view, Murai's work of carbonyl-directed Ru-catalyzed reaction using vinylsilanes is a monumental achievement.[3] Later, Rh- and Ir-catalyzed carbonyl-directed *ortho*-C-H alkylations of arenes followed.[4,5] Imino group is a potent directing group, and Rh-, Ru- and Co-catalyzed reactions with alkenes were reported.[6-8] Pyridyl group is more versatile: Co-, Ir- and Ru-catalyzed C-H alkylations were disclosed[9-11] and an enantioselective variant for the creation of planar chirality of ferrocenes was also achieved.[12] Efficient *ortho*-alkylation of phenol and anisole were also reported by a rhenium and yttrium catalyst, respectively.[13,14] 8-Quinolylcarbamoyl group was used as an efficient *N*,*N*-bidentate directing group in C-H alkylation.[15]

In contrast, pyridine *N*-oxides and its derivatives are fascinating substrates in the direct C-H functionalization, because of their high reactivity at the C2 position and facile removal of the oxygen atom by reduction.[16] Fagnou pioneeringly reported Pd-catalyzed C-H arylation of pyridine *N*-oxides by aryl halides.[17] He further developed site-selective sp^3 C-H arylation of 2-methylpyridine *N*-oxides, which gave 2-arylmethyl pyridine *N*-oxides (Scheme 1-a).[18] Recently, cross hydrogenative coupling was achieved with the use of relatively active C-H bonds in heteroaromatics.[19] However, as for the C-H alkylation of pyridine *N*-oxides using alkenes, there is only an example: Chang disclosed Rh-catalyzed reaction with electron-deficient alkenes in the presence of a stoichiometric amount of base (Scheme 1-b).[20,21] In this article, we show a cationic iridium-catalyzed C-H alkylation of 2-substituted pyridine *N*-oxides with acrylates (Scheme 1-c).



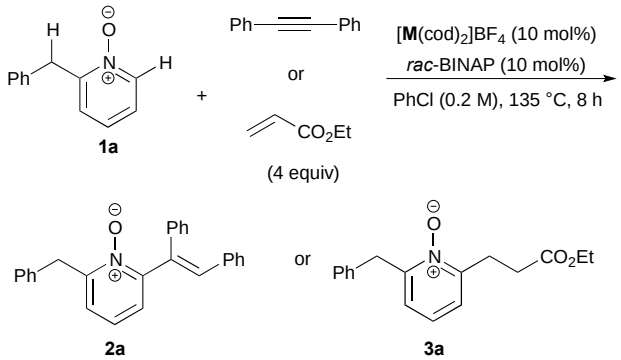
Scheme 1 C-H bond functionalization of pyridine *N*-oxides with aryl bromides and alkenes

Results and discussion

We recently reported the cationic Rh-catalyzed reaction of quinoline *N*-oxides with diphenylacetylene, where C-8 position-

selective alkenylation proceeded due to the directing effect of *N*-oxide moiety, and no C-2 alkenylated product was observed.[22] We got interested in the site-selectivity of *N*-oxides, and examined the reaction of 2-benzylpyridine *N*-oxide (**1a**)[18,23] with diphenylacetylene in the presence of cationic Rh- or Ir-*rac*-BINAP catalyst, but no alkenylated products were detected (entries 1 and 2 in Table 1). When the reaction with ethyl acrylate was conducted, C-6 alkylated product **3a** was obtained in the presence of the Ir catalyst in low yield, but the alkylated product at the benzylic position could not be detected at all (entries 3 and 4).

Table 1 Rh- or Ir-catalyzed reaction of 2-benzylpyridine *N*-oxide (**1a**)

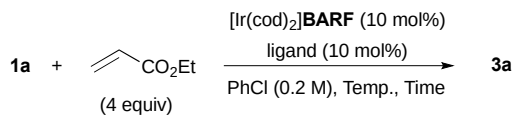


Entry	**M** cat.	Reagent	Yield (%)
1	Rh	diphenylacetylene	ND[a] (**2a**)
2	Ir	diphenylacetylene	ND[a] (**2a**)
3	Rh	ethyl acrylate	4 (**3a**)
4	Ir	ethyl acrylate	23 (**3a**)

[a] Not detected.

We next optimized the reaction conditions (Table 2). The effect of counter anion of iridium was significant: when tetrakis[3,5-bis(trifluoromethyl)phenyl]borate (BARF) was used, the yield was drastically improved to 65% (entry 2). After further ligand screening, biaryl skeleton was found to be important, and *rac*-BINAP was used for further investigations (entries 3-5). A slight increase of yield was observed when the reaction was examined in a screw-capped Schlenk flask in place of glass-stoppered one, due to the low boiling point of ethyl acrylate (entry 6). The reaction was sensitive to reaction temperature: the best yield of 88% was achieved at 120 ℃ for prolonged reaction time (entry 7). The reaction also proceeded at 100 ℃, but the yield was moderate after 48 h (entry 9). The Rh counterpart was ineffective in this reaction (entry 10).

Table 2 Screening of the reaction conditions

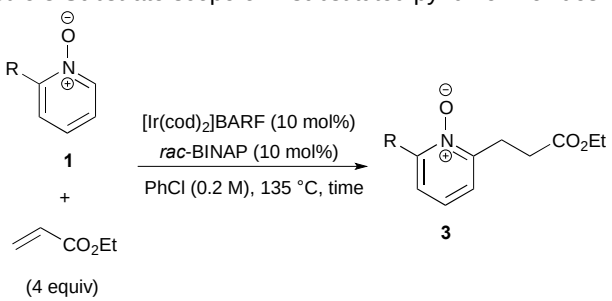


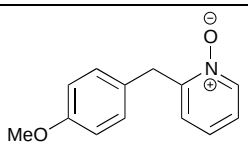
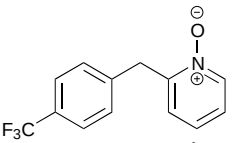
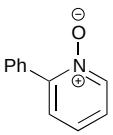
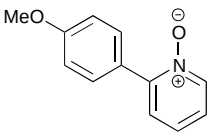
Entry	Ligand	Temp. (℃)	Time (h)	Yield (%)
1[a]	*rac*-BINAP	135	8	34
2	*rac*-BINAP	135	8	65
3	BIPHEP	135	8	32
4	DPPP	135	8	ND[b]
5	PPh_3	135	8	ND[b]
6[c]	*rac*-BINAP	135	8	70
7[c]	*rac*-BINAP	120	24	88
8[c]	*rac*-BINAP	100	24	42
9[c]	*rac*-BINAP	100	48	44
10[c,d]	*rac*-BINAP	120	24	ND

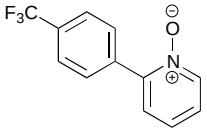
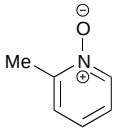
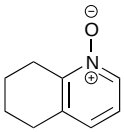
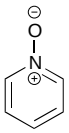
[a] Triflate was used as a counter anion of Ir catalyst. [b] Not detected. [c] Screw-capped Schlenk flask was used in place of glass-stoppered one. [d] $[Rh(cod)_2]$BARF was used in place of $[Ir(cod)_2]$BARF.

Under the reaction conditions of entry 7 in Table 2, several 2-substituted pyridine *N*-oxides **1** was subjected to the reaction with ethyl acrylate (Table 3). Both electron-donating and -withdrawing group-substituted 2-benzylpyridine *N*-oxides **1b** and **1c** could be transformed into the corresponding 2,6-disubstituted products **3b** and **3c**, respectively (entries 1 and 2). 2-Aryl-substituted pyridine *N*-oxides were also good substrates, and electron-donating and -withdrawing groups were tolerable at the para position (entries 3-5). 2-Methylpyridine *N*-oxide (**1g**) and 5,6,7,8-tetrahydroquinoline *N*-oxide (**1h**) also reacted smoothly to give the desired products in high yields (entries 6 and 7).[24,25] Interestingly, the reaction using non-substituted pyridine *N*-oxide (**1i**) gave the desired monoalkylated product **3i**, yet in low yield without the formation of dialkylated product (entry 8). The reaction was messy and **1i** was not completely consumed.[26]

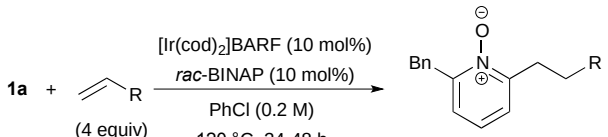
Table 3 Substrate scope of 2-substituted pyridine *N*-oxides **1**



Entry	*N*-oxide	Time (h)	Yield (%)
1	 **1b**	48	67 (**3b**)
2	 **1c**	24	75 (**3c**)
3	 **1d**	24	79 (**3d**)
4	 **1e**	24	82 (**3e**)

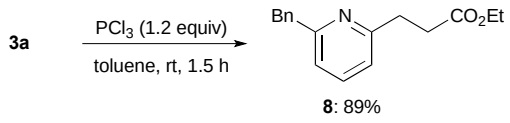
5	 **1f**	48	73 (**3f**)
6	 **1g**	48	75 (**3g**)
7	 **1h**	24	78 (**3h**)
8	 **1i**	48	18 (**3i**)

The reaction of *N*-oxide **1a** with *tert*-butyl acrylate also proceeded (Scheme 2). But the reaction with methyl vinyl ketone and phenyl vinyl sulfone was messy and the yield of alkylated products **5a** and **6a** was low. When styrene was used, only a trace amount of product **7a** was detected.



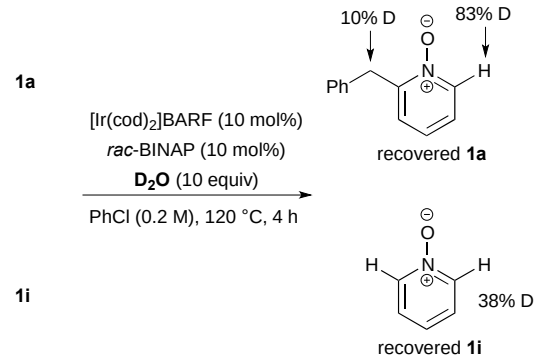
Scheme 2 Reaction with other alkenes

Reduction of alkylated product **3a** using trichlorophosphine proceeded smoothly at room temperature to afford 2,6-unsymmetrically disubstituted pyridine **8** in high yield (Scheme 3).



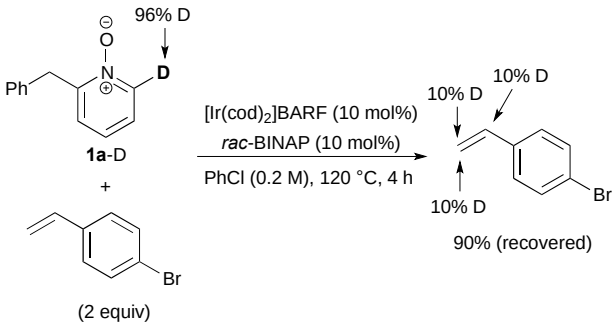
Scheme 3 Reduction of alkylated product **3a**

As a preliminary mechanism study, the *N*-oxides were subjected to otherwise similar conditions, in the presence of excess amounts of D_2O and in the absence of ethyl acrylate, then D-content of the recovered *N*-oxides was measured (Scheme 4). In the case of **1a**, high degree of deuteration at the C2 position and low degree of deuteration at the benzylic position were observed. Also in the case of **1i**, deuteration was observed. These results suggest that C-H bond cleavage adjacent to the *N*-oxide surely occurred whether there is a substituent at the C2 position or not.



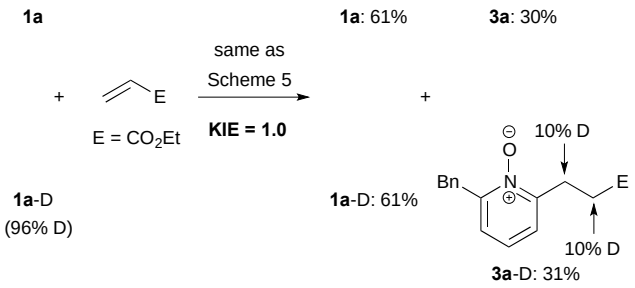
Scheme 4 Reaction in the presence of D_2O

We next examined the reaction of deuterated **1a**-D with *p*-bromostyrene (Scheme 5). Although no C6-alkylated product was detected, but deuterium incorporation into both of α- and β-positions of the recovered styrene was ascertained. These results indicate that C-H bond cleavage and alkene insertion proceeded, but subsequent reductive elimination did not proceed in the reaction with styrene.



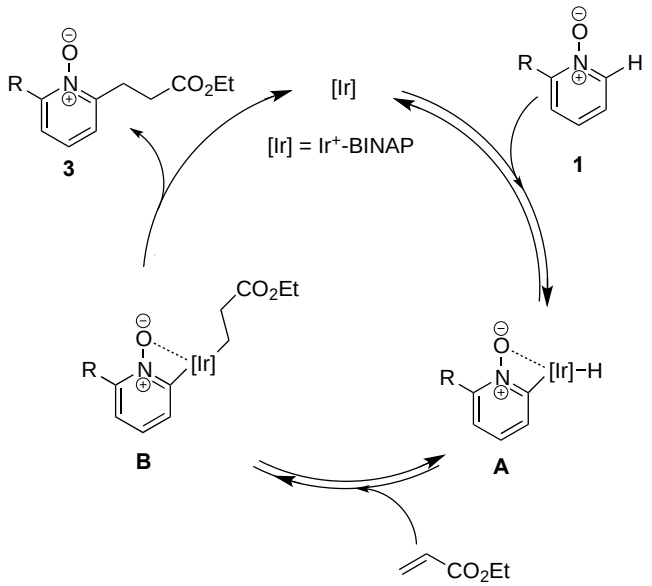
Scheme 5 Reaction of deuterated *N*-oxide **1a**-D with *p*-bromostyrene

Finally, we measured kinetic isotope effect (KIE) of the present cationic Ir-catalyzed C-H alkylation by two parallel experiments using **1a** and **1a**-D, respectively (Scheme 6). The reactions were quenched after 4 h. The KIE value was ca. 1.0 based on the yield ratio of **3a**-D/**3a**. Moreover, the deuterium incorporation into both α- and β-positions of ester moiety of the product **3a**-D was observed. These results suggest that both C-H bond cleavage and alkene insertion are reversible steps, and that the reductive elimination would be a rate-determining step, which is contrasting to the C-H alkylation using the combination of neutral Rh catalyst and base (KIE value = 3.2).[20]



Scheme 6 KIE measurement by two parallel experiments

The proposed mechanism was depicted in Scheme 7. We assumed that the C-H bond cleavage is assisted by the coordination of *N*-oxide to Ir center and intermediate **A** was formed.[28] Subsequent hydroiridation to acrylate provides intermediate **B**, but the pathway of carboiridation cannot be excluded. Finally, reductive elimination gives a linear alkylated product and only the final step may be irreversible.



Scheme 7 Proposed mechanism of C-H alkylation

Conclusions

The cationic Ir catalyst combining with *rac*-BINAP ligand realized C-H alkylation of 2-substituted pyridine *N*-oxides with acrylates. Pd-catalyzed C-H arylation and subsequent Ir-catalyzed C-H alkylation provides a facile synthetic protocol for the preparation of 2,6-unsymmetrically disubstituted pyridine derivatives. The preliminary mechanism study revealed that the steps of C-H bond cleavage and alkene insertion are reversible.

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Notes and references

[a] Department of Chemistry and Biochemistry, School of Advanced Science and Engineering, Waseda University, Shinjuku, Tokyo 169-8555, Japan, Fax: (+81) 3-5286-8098; e-mail: tshibata@waseda.jp
[b] JST, ACT-C, 4-1-8 Honcho, Kawaguchi, Saitama 332-0012, Japan.

† Dedicated to Professor Ei-ichi Negishi on the occasion of his 80th birthday

‡ Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/c000000x/

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24 The reaction of quinoline *N*-oxide was messy and the alkylated product could not be detected, but quinoline was detected as a reduced product.
25 In each entry of Table 3, a small amount of reduced 2-substituted pyridine was obtained as a by-product.
26 The reaction of 4-phenylpyridine *N*-oxide gave the corresponding alkylated product in low yield (4%).
27 Substituted acrylates, such as ethyl methacrylate, ethyl cinnamate, and (*E*)-ethyl penta-2,4-dienoate, were inactive in this reaction.
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